IV ZOOM Journal Club 2014

Gruppo di Studio per la Patologia Mammaria

I margini di resezione:

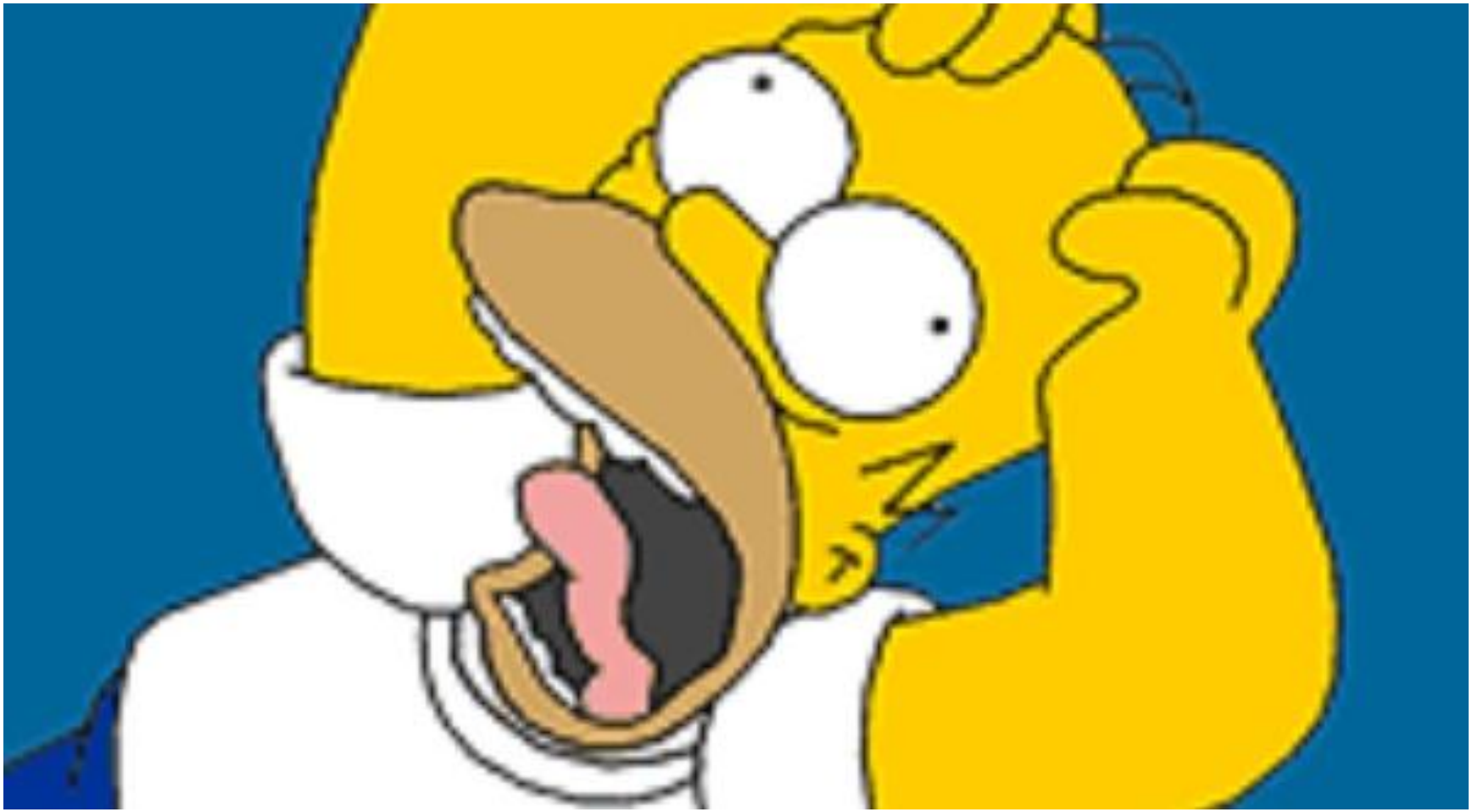
Impatto sulla gestione radioterapica

Discussant

Ivan Fazio

Bologna, 20 Febbraio 2015
Hotel NH De La Gare

casa di cura macchiarella S.p.A.



What we really search in the literature?

- Confirmation of the exactness in our daily work;

- Certainties if we're changing our daily work;

Margins in Breast Conservation: A Clinician's Perspective and What the Literature Tells Us

NEHMAT HOUSSAMI, MBBS, PhD[1,2] AND MONICA MORROW, MD[3,4]*

A new but old "affair"

- Negative margin as the main goal in surgical resection;

- Negative margin as ancillary result in "oncoplastic program";

Journal of Surgical Oncology 2014;110:2–7

Margins in Breast Conservation: A Clinician's Perspective and What the Literature Tells Us

NEHMAT HOUSSAMI, MBBS, PhD[1,2] AND MONICA MORROW, MD[3,4]*

- Negative margin is the absence of tumor cells on ink margin.

- " a negative margin doesn't preclude the presence of residual disease, but a negative margin identifes a population of patients with a residual disease burden that is small enough that is likely to be controlled by radiotherapy."

- Tumor burden is not the primary determinant of local control (LR in mastectomy).

- The introduction of "minimal negative margin" will reduce the use of re-excision.

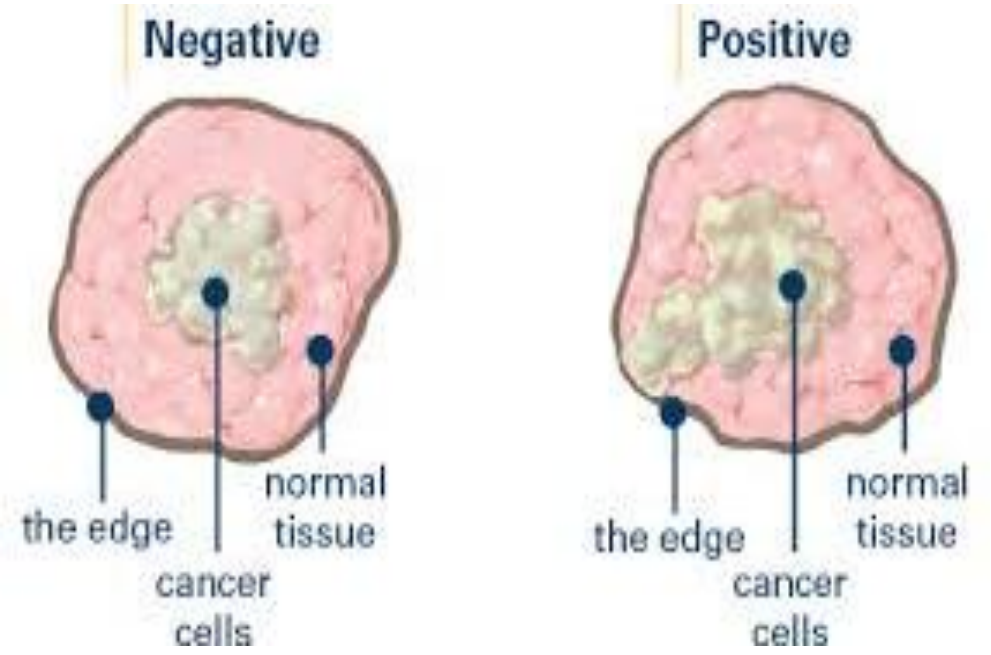
- Relationship between LR,TN and patient age

Journal of Surgical Oncology 2014;110:2–7

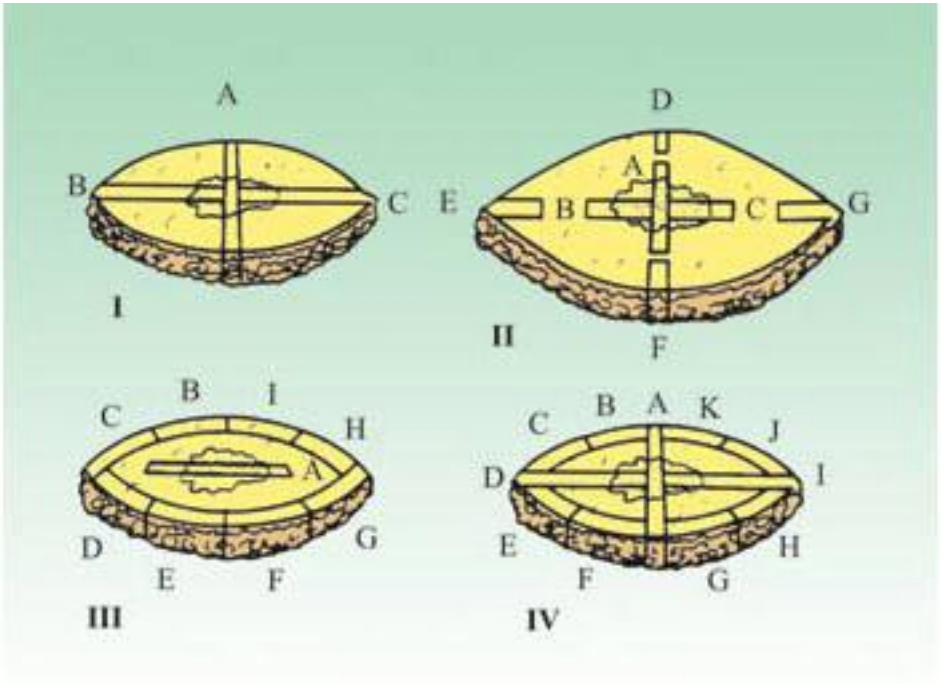
Margins in Breast Conservation: A Clinician's Perspective and What the Literature Tells Us

NEHMAT HOUSSAMI, MBBS, PhD[1,2] AND MONICA MORROW, MD[3,4]*

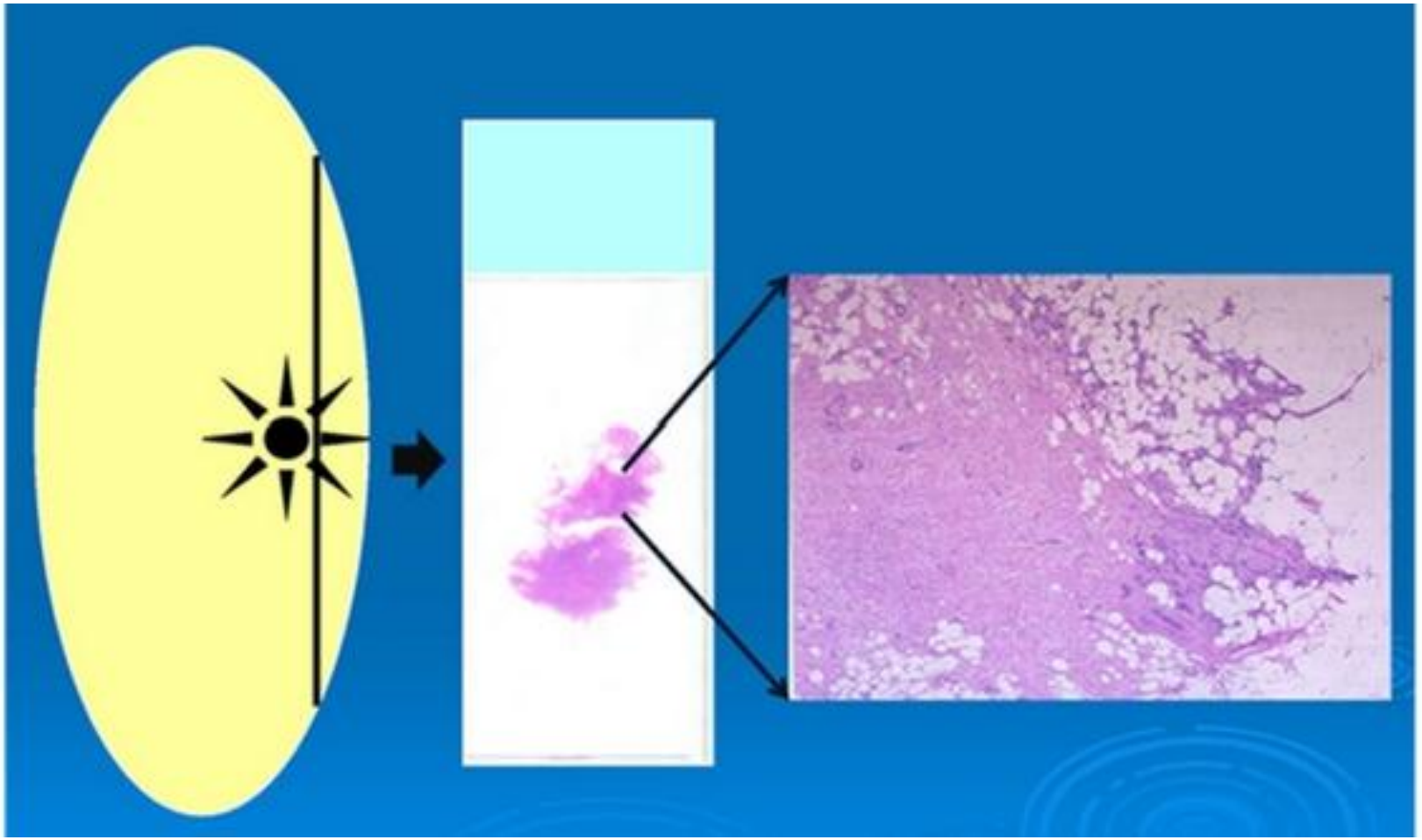
- Radial and shaved margins.



Radial margin



Shaved margin



No way to know the distance between the negative margin and the closer tumoral cells

J Am Coll Surg. 2007 Apr;204(4):541-9

Perpendicular inked versus tangential shaved margins in breast-conserving surgery: does the method matter?

Wright MJ1, Park J, Fey JV, Park A, O'Neill A, Tan LK, Borgen PI, Cody HS 3rd, Van Zee KJ, King TA.

- The rate of reported "positive" margins was significantly higher in “Shaved Margins” (49%) versus (16%), of “ink margins”.
- In shaved margins there are only positive or negative margins
- The likelihood of finding residual disease remained the same (27% versus 32%, p=NS).

Margin examination

- The specimen could be not correctly evaluated because of the changing in shape and consistency after lumpectomy.

- The ink used for the specimen could truck to the deeper part of the specimen giving the idea of a closer margin than real one.

Role of systemic therapy

- The introduction of trastuzumab in HER-2 enriched patient seems to reduce of about 50% the incidence of LR independent of type of surgery, use of radiotherapy or menopausal state.

Bouganim N, Tsvetkova E, Clemons M, et al.: Evolution of sites of recurrence after early breast cancer over the last 20 years: Implications for patient care and future research. Breast Cancer Res Treat 2013;139:603–606.

World J Surg (2014) 38:2279–2287
DOI 10.1007/s00268-014-2596-x

World Journal of Surgery

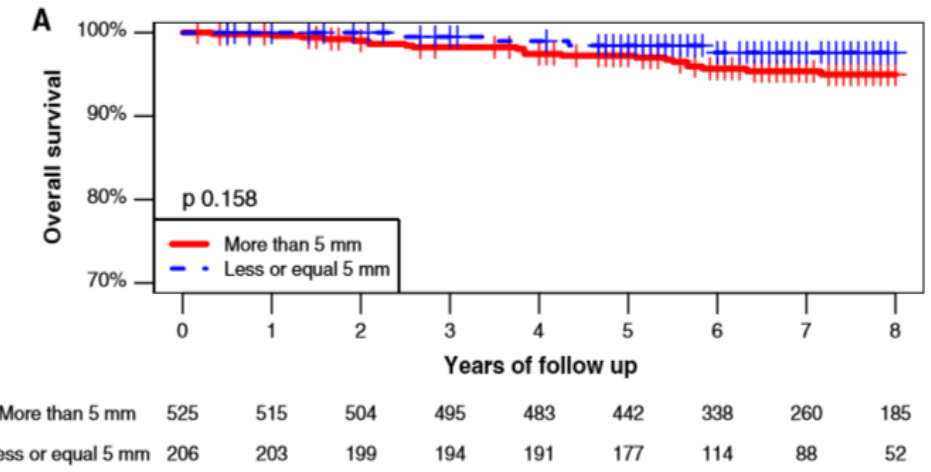
Influence of Surgical Margins on the Outcome of Breast Cancer Patients: A Retrospective Analysis

Sergio Bernardi · Serena Bertozzi · Ambrogio P. Londero · Giuliana Gentile · Vito Angione · Roberto Petri

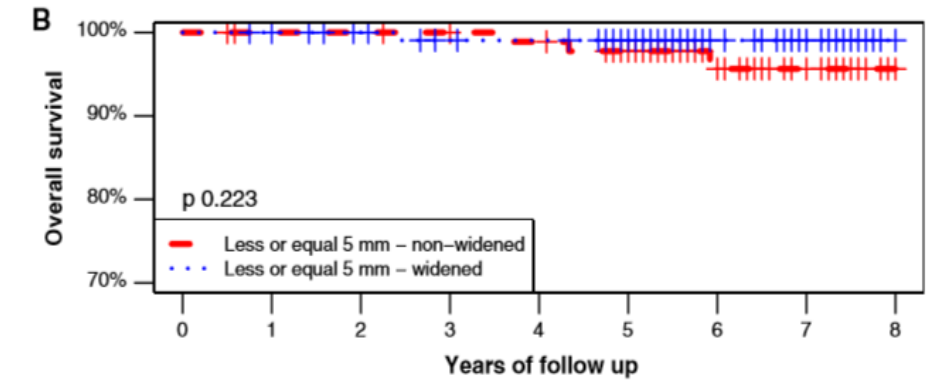
- "discussion: Our clinical experience has highlighted the importance of of sensitizing patients to their life-lonf risk of LR, which is of about 2-7% for patients with final negative margins, bur increases to as high as 22% for patients with positive margins.

- "Conclusions: we found the status of resection margins and the management of infiltrated or narrow margins to have no significant influence on local tumor recurrence rates or on overall patient survival". Instead biological factors connected with tumor aggressiveness, seems to play the most important role in breast cancer prognosis independent of surgical radicality

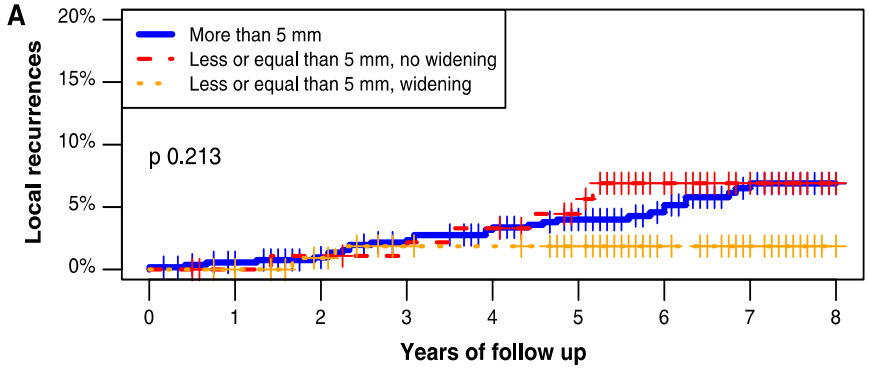
? ? ?



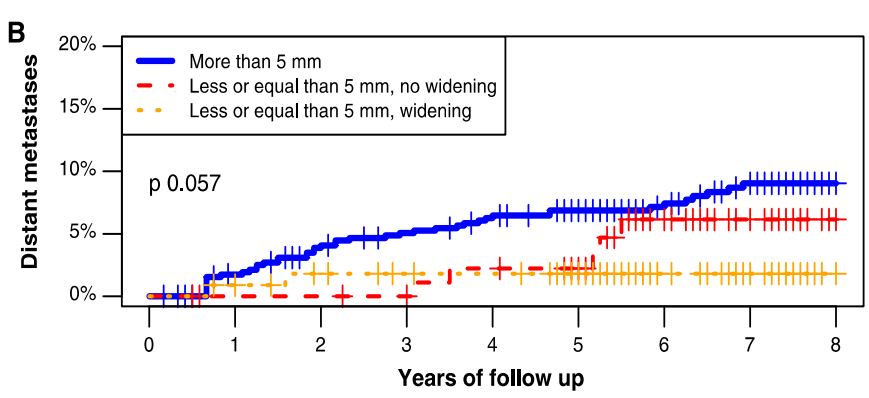
More than 5 mm	525	515	504	495	483	442	338	260	185
ess or equal 5 mm	206	203	199	194	191	177	114	88	52



Non–widened	94	92	92	91	89	83	45	31	12
Widened	112	111	107	103	102	94	69	57	40



More than 5 mm	525	513	500	487	472	427	323	242	171
<5 mm, no widening	94	92	91	90	86	80	43	30	11
<5 mm, widening	112	111	106	101	100	92	68	56	39



More than 5 mm	525	508	490	479	465	425	328	246	175
<5 mm, no widening	94	92	92	91	88	84	45	31	12
<5 mm, widening	112	110	105	102	101	93	69	57	40

The entire population of the study has been devided in multiple subpopulations even more narrow.

World J Surg (2014) 38:2279–2287
DOI 10.1007/s00268-014-2596-x

World Journal of Surgery

Influence of Surgical Margins on the Outcome of Breast Cancer Patients: A Retrospective Analysis

Sergio Bernardi · Serena Bertozzi · Ambrogio P. Londero · Giuliana Gentile · Vito Angione · Roberto Petri

	A, Total population		B, Patients without re-operation	
	OR (95 % CI)	*p* value	OR (95 % CI)	*p* value
Grading (G3)	2.32 (0.89–6.04)	0.085	2.09 (0.8–5.49)	0.135
Ki-67/Mib-1 >20	7.08 (2.08–24.07)	<0.05	6.96 (2.02–24.01)	<0.05
Triple negative cancer	1.88 (0.69–5.13)	0.219	1.9 (0.68–5.28)	0.219
Comedo-like necrosis	18.51 (3.34–102.6)	<0.05	15.89 (2.58–97.82)	<0.05
Multifocality	5.18 (1.53–17.58)	<0.05	5.8 (1.71–19.73)	<0.05
Extensive intra-ductal component	0.52 (0.15–1.84)	0.314	0.59 (0.16–2.16)	0.429
Peritumoral inflammation	2.17 (0.51–9.31)	0.297	2.49 (0.61–10.21)	0.205
Tumor size >2 cm	1.27 (0.47–3.46)	0.635	1.43 (0.51–3.98)	0.497
Axillary lymph node positivity	0.74 (0.27–2.02)	0.553	0.74 (0.26–2.05)	0.559
Non-axillary lymph node positivity	10.57 (2.24–49.9)	<0.05	5.61 (0.94–33.65)	0.059
Extracapsular invasion of lymph node metastasis	1.46 (0.28–7.59)	0.649	2.1 (0.39–11.37)	0.387
Margin status				
Positive margin	Reference	1.000	Reference	1.000
Free margin between 0 and ≤2 mm	0.88 (0.06–12.55)	0.928	0.55 (0.01–24.26)	0.759
Free margin between 2 and ≤5 mm	5.11 (0.59–44.54)	0.140	3.3 (0.1–104.62)	0.498
Free margin >5 mm	3.35 (0.59–18.99)	0.172	1.28 (0.06–29.05)	0.879

- The reoperation rate due to a margin less than 5mm was higher in patients with lesions idetified by ROLL compared with palpable lesions (23% Vs. 10%)

Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1006e1014, 2014

Clinical Investigation

Pattern of Ipsilateral Breast Tumor Recurrence After Breast-Conserving Therapy

Jan Jobsen, PhD,* Job van der Palen, PhD,†,‡ Sietske Riemersma, PhD,§ Harald Heijmans, MD,‖ Francisca Ong, PhD,* and Henk Struikmans, PhD¶,#

Retrospective study ranging from 1984 to 2010 (27 years!!):

- Is it an homogeneous and comparable population? (adjuvant treatments)
- Is it possible to imagine comparable examining thechniques for pathology?
- Large difference in population of “no recurrence” patients an “recurrence” ones

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Harald Heijmans, MD,‖ Francisca Ong, PhD,* and Henk Struikmans, PhD¶,#

- All patients underwent PORT (50 Gy in 25f.) followed by a boost of 14 Gy regardless of MS;
- Only in 16% slightly altered boost doses were administred;
- Since 2004 boost was administred depending on age, N status, margin status;
- Regional RT was indicated for patients with more than 4 positive nodes or extranodal involvement.

Clinical Investigation

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Int J Radiation Oncol Biol Phys, Vol. 89, No. 5, pp. 1006e1014, 2014

Table 1 Patient and tumor characteristics of 3963 cased of BCT in 3828 women at primary diagnosis according to status local control*

Characteristic	No local recurrences (n = 3779) (%)	Local recurrences (n = 184) (%)	*P* value†
Age (y)			
≤40	201 (5.2)	31 (16.8)	<.001
41-50	793 (20.9)	51 (27.7)	
>50	2785 (73.9)	102 (55.4)	
Family history			
Positive	922 (24.3)	41 (22.3)	NS
Negative	2843 (75.3)	142 (77.2)	
Unknown	14 (0.4)	1 (0.5)	
Histology			
Ductal carcinoma	3065 (81.3)	135 (73.4)	
Lobular carcinoma	385 (10.1)	28 (15.2)	
Medullar carcinoma	49 (1.3)	5 (2.7)	NS
Tubular carcinoma	190 (5.0)	10 (5.4)	
Other	90 (2.3)	6 (3.3)	
Malignancy grade			
1	874 (23.1)	41 (22.3)	
2	1450 (38.4)	80 (43.5)	NS
3	808 (21.4)	55 (29.9)	
Unknown	647 (17.1)	8 (4.4)	
Lymph vascular space invasion			
Positive	332 (8.8)	31 (16.8)	
Negative	3425 (90.6)	152 (82.6)	<.001
Unknown	22 (0.6)	1 (0.6)	
Presence of CIS			
DCIS	1013 (26.8)	49 (26.6)	
LCIS	204 (5.4)	20 (10.9)	.006
None	2562 (67.8)	115 (62.5)	
Mitotic activity index			
Low (≤13 in 2 mm^2)	1921 (50.8)	120 (65.2)	
High (>12 in 2 mm^2)	899 (23.7)	49 (26.6)	NS
Unknown	959 (25.5)	15 (8.2)	
Hormone receptor			
ERPR positive	2427 (64.2)	129 (70.1)	
ERPR negative	516 (13.7)	27 (14.7)	NS
ER positive and PR negative	514 (13.6)	17 (9.2)	
ER negative and PR positive	73 (1.9)	6 (3.3)	
Unknown	249 (6.6)	5 (2.7)	
HER 2 status			
Positive	113 (3.0)	6 (3.3)	
Negative	1310 (35.1)	137 (74.5)	NS
Unknown	2325 (61.9)	41 (22.3)	
Re-excision			
Yes	265 (7.0)	13 (7.1)	
None	3497 (92.5)	168 (91.3)	NS
Unknown	17 (0.5)	3 (1.6)	
Margin status			
Negative	3343 (88.4)	148 (80.4)	
Positive IC	259 (6.9)	19 (10.3)	.008
Positive DCIS	137 (3.7)	13 (7.2)	
Positive IC + DCIS	40 (1.1)	4 (2.2)	
Tumor size			
pT1	2894 (76.4)	136 (73.9)	
pT2	875 (23.3)	48 (26.1)	NS
Other	10 (0.3)	0	
Lymph node status			

Young age is the most important risk factor for LR, but negative margin should be made a prerequisite for completing BCT

Journal of Breast Cancer

J Breast Cancer 2014 December; 17(4): 301-307 http://dx.doi.org/10.4048/jbc.2014.17.4.301

REVIEW ARTICLE

Unique Features of Young Age Breast Cancer and Its Management

Han-Byoel Lee[1], Wonshik Han[1,2]

- Retrospective study but large population (11.000 patients)

Considerations	Unique features
Biological characteristics	Higher proliferation rates (Ki-67), more grades 3/4 & higher ER negativity [9-13]
	More BRCA1/2 mutations [22-32]
Diagnostic delay	More advanced stage at presentation [33-35]
Prognosis	Worse in ER-positive breast cancer [14,40-42]
	5% increased risk of death/1-year reduction in age [7]
Local therapy	More IBTR [43-47]
	Higher importance of sufficient resection margins [52]
	Boost radiotherapy should be considered [47]
Adjuvant chemotherapy	Less chemotherapy-induced amenorrhea [41-42]
	Greater benefits from chemotherapy [58-59]
Adjuvant hormonal therapy	Tamoxifen resistance [14]
Others	Premature ovarian failure and infertility [66-69]
	More emotional distress and poorer quality of life [72,73]

Journal of Breast Cancer
J Breast Cancer 2014 December; 17(4): 301-307 http://dx.doi.org/10.4048/jbc.2014.17.4.301
CrossMark click for updates
REVIEW ARTICLE

Unique Features of Young Age Breast Cancer and Its Management

Han-Byoel Lee[1], Wonshik Han[1,2]

- Women ≤ 45 aa. with resection margins ≤2 mm had local failure rates of 19% whereas those with wider margins had a local failure rate of 7%.
- This difference was not significative in women older than 45aa.

Journal of Breast Cancer
J Breast Cancer 2014 December; 17(4): 301-307 http://dx.doi.org/10.4048/jbc.2014.17.4.301
REVIEW ARTICLE

Unique Features of Young Age Breast Cancer and Its Management

Han-Byoel Lee[1], Wonshik Han[1,2]

Int J Radiat Oncol Biol Phys. 2009 Mar 1;73(3):734-44. doi: 10.1016/j.ijrobp.2008.04.078. Epub 2008 Aug 15.

Ten-year recurrence rates in young women with breast cancer by locoregional treatment approach.

Beadle BM1, Woodward WA, Tucker SL, Outlaw ED, Allen PK, Oh JL, Strom EA, Perkins GH, Tereffe W, Yu TK, Meric-Bernstam F, Litton JK, Buchholz TA.

Ann Surg Oncol. 2014 Feb;21(2):395-400. doi: 10.1245/s10434-013-3319-5. Epub 2013 Oct 22.

Postmastectomy radiation and recurrence patterns in breast cancer patients younger than age 35 years: a population-based cohort.

Quan ML1, Osman F, McCready D, Fernandes K, Sutradhar R, Paszat L.

In patients younger than 35 years old, treated with mastectomy for stage II BC, the addition of radiotherapy results in a significant improvement in local recurrence rates (about 40%) but failed to show a survival benefit

Cancer. 2003 Jan 1;97(1):30-9.

Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy.

Neuschatz AC1, DiPetrillo T, Safaii H, Price LL, Schmidt-Ullrich RK, Wazer DE.

Department of Radiation Oncology #359, Tufts-New England Medical Center, Boston, MA 02111, USA. aneuschatz@lifespan.org

On multivariate analysis, young age (P = 0.03) predicted increased local failure rate, whereas margins that were less than or equal to 2 mm or positive predicted late (> 5 years) but not early (< or = 5 years) recurrence (P = 0.003).

Graded tumor bed dose escalation in response to FMS results in very low rates of local failure over the first 5 years for all FMS categories.

“however,tumors with close/positive margins have significantly increased local failure rates after 5 years of follow-up even with increased radiation boost dose. In addition, graded tumor bed dose escalation does not fully overcome the adverse influence of young age.”

Clinical Investigation: Breast Cancer

Is Biological Subtype Prognostic of Locoregional Recurrence Risk in Women With pT1-2N0 Breast Cancer Treated With Mastectomy?

Pauline T. Truong, MDCM,*,† Betro T. Sadek, MD,‡ Maria F. Lesperance, BSc,* Cheryl S. Alexander, CHIM,† Mina Shenouda, MD,‡ Rita Abi Raad, MD,‡ and Alphonse G. Taghian, MD, PhD‡

- No patients received PMRT (pt1-2 N0) and the end point is to assess if is possible to identify high risk women who can benefit from PMRT;

- There is not a subtype correlated with increase of LRR but patients TN together with positive margin, could be considered suitable for PMRT;

- 5 years follow up is too short considering other studies which demonstrated higher rates of local recurrence after 5 years.

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and Alphonse G. Taghian, MD, PhD‡

Subtypes: luminal A: ER+ or PR+/HER 2/grade 1-2;
luminal B: ER+ or PR+/HER 2/grade 3;
luminal HER 2: ER+ or PR+/HER 2+;
HER 2 enriched: ER-/ PR-/HER 2+;
triple-negative breast cancer (TNBC): ER-/PR-/HER 2-

1 death is prevented for every 4 local recurrences avoided in high risk patients
(the benefit is less important due to distant mets)

1 death is prevented for each local recurrence avoided in low risk patients
(how many patients we have to treat to prevent a local recurrece?)

Ann Surg Oncol (2014) 21:1209–1214
DOI 10.1245/s10434-013-3416-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Effect of Margin Width on Local Recurrence in Triple-Negative Breast Cancer Patients Treated with Breast-Conserving Therapy

Melissa Pilewskie, MD[1], Alice Ho, MD[2], Emily Orell, BS[1], Michelle Stempel, MPH[1], Yu Chen, BS[3], Anne Eaton, MS[4], Sujata Patil, PhD[4], and Monica Morrow, MD[1]

Retrospective study (1999 – 2009)

FU: 84m;
37 LR, 18 RR and 77 DR
Aggressive disease!

TABLE 1 Patient and treatment variable by margin status

Variable	Margin of		*p* value
	≤2 mm ($n = 71$)	>2 mm ($n = 464$)	
Age at surgery (mean ± standard deviation)	56.7 ± 12.2	55.2 ± 12.2	0.30
Age >50 years	53 (75 %)	312 (67 %)	0.27
Tumor size, median (IQR)	1.5 (1–2.2)	1.6 (1.1–2.3)	0.27
Tumor size >2 cm	22/69 (32 %)	165/457 (36 %)	0.59
Lymphovascular invasion present	19 (27 %)	110 (24 %)	0.55
Nodal status positive	25/71 (35 %)	130/463 (28 %)	0.26
Chemotherapy	54 (76 %)	398 (86 %)	0.05
Whole-breast RT[a]	68 (96 %)	457 (98 %)	0.14
Tumor bed boost[b]	59/63 (94 %)	380/405 (94 %)	1.00
Regional RT[b]	10/62 (16 %)	41/404 (10 %)	0.19

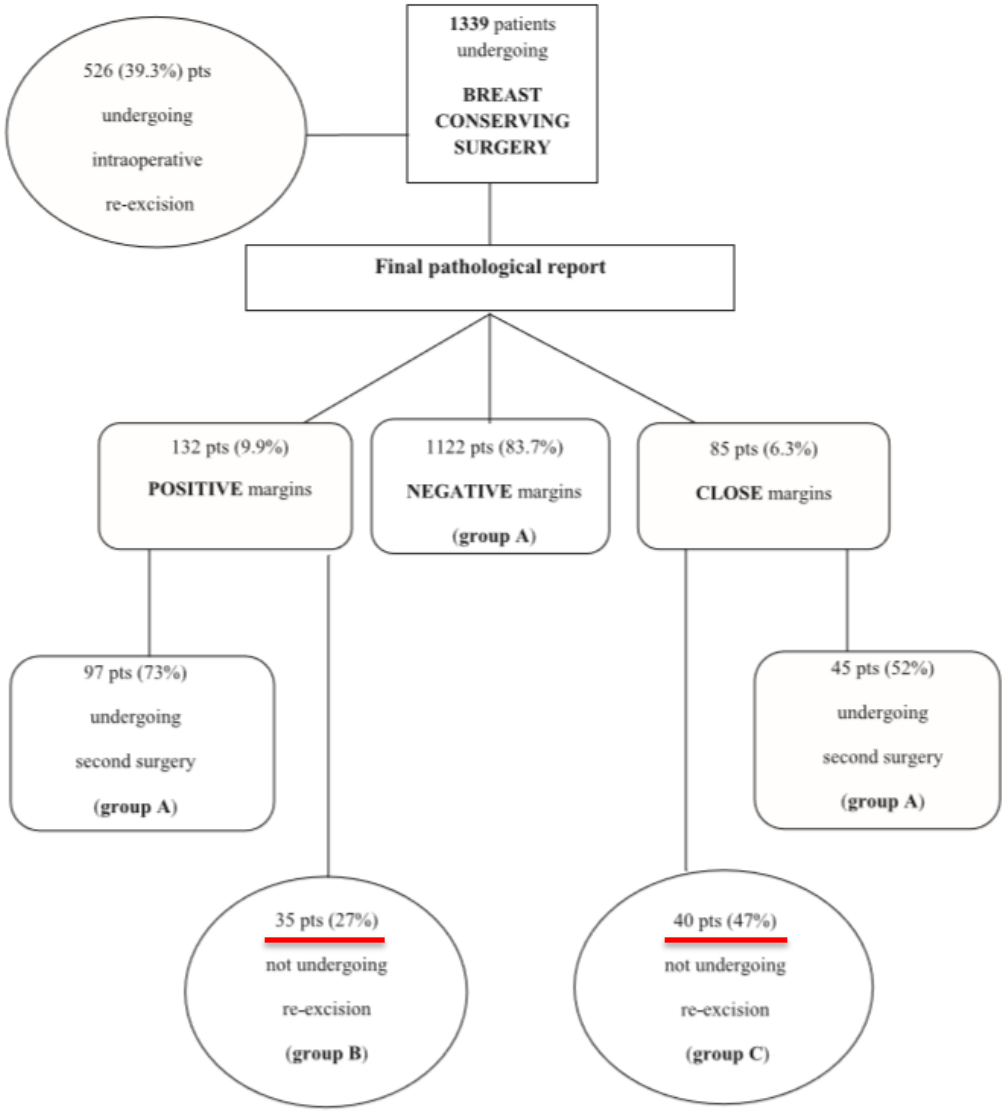
This study suggest that in TNBC the difference in terms of LR, if the margin width is ≤2mm or > 2mm, is not significative.

Patients with positive margins were excluded but It could be interesting to know the behavior of TNBC's in case of m+

Role of re-excision for positive and close resection margins in patients treated with breast-conserving surgery

N. Biglia [a,*], R. Ponzone [b], V.E. Bounous [a], L.L. Mariani [a], F. Maggiorotto [b], C. Benevelli [a], V. Liberale [a], M.C. Ottino [a], P. Sismondi [a]

- Positive margin is the strongest risk predictor for LR;
- No difference for different width of close margins
- The HER-2 group and the TN group shows the the higher rate of LR while the Luminal A group has the lowest one



Role of re-excision for positive and close resection margins in patients treated with breast-conserving surgery

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- When the re-excision was suggested at radiological evaluation, the re-excision specimen was more often interested by in situ tumor (16%), compared to re-excisions indicated by the surgeon (9%) or by the pathologist (9%).

VOLUME 32 · NUMBER 14 · MAY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ONCOLOGY GRAND ROUNDS

Too Much, Too Little, or Just Right? Tumor M in Women Undergoing Breast-Conserving Sur

Kelly K. Hunt and Aysegul A. Sahin, *The University of Texas MD Anderson Cancer Center, Houston, TX*

Table 1. Reasons to Consider Re-Excision

Tumor at the inked margin
Significant discrepancy between radiographic and pathologic tumor size with multiple close margins
Scattered foci of DCIS or invasive cancer near multiple margins
Cautery artifact within ductal tissue at the margin with foci of DCIS or invasive cancer approaching the margin

Lobular histology and **DCIS** pose particular challenges for margin assessment and management.

Another problematic area is that of **extensive intraductal component**. Multiple close margins demonstrating DCIS are often cause for concern.

The evidence does not support wider margins or more extensive surgery on the basis of aggressive **biologic subtypes** such as triplenegative disease and HER2-positive disease. Although hormone receptor–negative breast cancers appear to be less sensitive to radiation therapy, the use of mastectomy does not result in significantly lower local failure rates.

Young age at breast cancer diagnosis is also associated with more aggressive disease;however,wider negative margins do not appear to significantly reduce the risk for local recurrence over a negative margin (“no ink on tumor”)

Younger patients may be at risk for carrying mutations in the breast cancer–associated genes (**BRCA1 and BRCA2**), and genetic counseling and genetic testing may be warranted. In the case of a BRCA mutation, breast conservation is not the preferred approach.

VOLUME 32 · NUMBER 14 · MAY 10 2014

JOURNAL OF CLINICAL ONCOLOGY ONCOLOGY GRAND ROUNDS

Too Much, Too Little, or Just Right? Tumor Margins in Women Undergoing Breast-Conserving Surgery

Kelly K. Hunt and Aysegul A. Sahin, *The University of Texas MD Anderson Cancer Center, Houston, TX*

Case 3

A 54-year-old female underwent a screening mammogram that revealed a new focal asymmetry in the left breast upper hemisphere at 12 o'clock located 7 cm from the nipple. Ultrasound revealed a suspicious hypoechoic mass measuring 1.3 × 1.0 × 0.7 cm correlating with the area of mammographic concern. A core biopsy demonstrated invasive ductal carcinoma grade 3. The tumor was ER negative, PgR negative, and HER2 negative. The patient underwent left breast wire-localized segmental mastectomy with sentinel node biopsy. The pathology revealed invasive ductal carcinoma measuring 2.5 cm in the largest dimension. There was adjacent high-grade, solid-type DCIS with central necrosis. Invasive tumor extended to 1.5 mm from the inked margin at a single focus (Fig 3). The remaining margins were widely free of tumor. Three sentinel lymph nodes were negative for metastatic disease.

The patient had a T2N0, high-grade, triple-receptor–negative breast cancer in the left breast with excision revealing tumor close to the inked margin focally in only one section. There was also high-grade DCIS adjacent to the invasive cancer. Adjuvant chemotherapy and radiotherapy are indicated. The preoperative imaging, intraoperative assessment with specimen radiograph, and histologic assessment were all consistent with a unifocal breast cancer that has been completely excised. The possibility of finding residual tumor in the breast is quite low, and we would not recommend re-excision in this patient.

Case 4

A 77-year-old woman had a screening mammogram that revealed a left-breast abnormality. A diagnostic bilateral mammogram revealed an area of architectural distortion measuring 2.4 cm in the posterior region of the left breast, upper outer quadrant at 1 o'clock, 9 cm from the nipple. There were no abnormalities in the right breast. Ultrasound of the left breast identified an area of architectural distortion in the 1 o'clock position, 9 cm from the nipple measuring 2.2 × 2.2 × 0.9 cm. There was no evidence of multifocal or multicentric disease. There were scattered fibrocystic changes noted in the remaining left breast. No evidence of regional lymphadenopathy was identified. Ultrasound-guided core biopsy revealed invasive mammary carcinoma with mixed ductal and lobular features grade 2, strongly positive for ER and PgR and negative for HER2. The patient underwent left breast needle-localized segmental mastectomy, intraoperative lymphatic mapping, and sentinel lymph node biopsy. The pathology revealed invasive carcinoma grade 2 with predominantly lobular features. Invasive tumor was seen throughout the largest dimension of the specimen measuring approximately 7 cm in greatest dimension. Invasive tumor was seen within 0.5 mm of the inked inferior margin and was less than 1 mm from the anterior/superior and the posterior margins (Fig 4). One sentinel lymph node was negative for metastatic disease. In this case the preoperative imaging significantly underestimated the size of the tumor and extent of disease in the breast. On the basis of the preoperative tumor size, hormone receptor status, and age of the patient, consideration was given for surgical excision followed by adjuvant endocrine therapy without the need for radiation. Although there was no ink on the tumor, because of the finding of several close margins and the discrepancy between clinical and pathologic tumor size, the likelihood of having residual tumor is high, and we recommend re-excision.

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JOURNAL OF CLINICAL ONCOLOGY

ONCOLOGY GRAND ROUNDS

Too Much, Too Little, or Just Right? Tumor Margins in Women Undergoing Breast-Conserving Surgery

Kelly K. Hunt and Aysegul A. Sahin, *The University of Texas MD Anderson Cancer Center, Houston, TX*

- "the goal of breast conserving therapy is to remove the primary tumor with negative margins but to preserve the shape and the size of the breast for an optimal long term cosmetic outcome."

- The adequacy of negative margin depends on: tumor focality, extent of affected margin, planned sistemic therapy and radiotherapy, surgical opportunities of re-excision without the need for mastectomy.

- The increased risk of LR in Her-2 and TN patients is not mitigated by wider margins or more aggressive surgical resection

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ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD[1], Stuart J. Schnitt, MD[2], Armando E. Giuliano, MD[3], Jay R. Harris, MD[4], Seema A. Khan, MD[5], Janet Horton, MD[6], Suzanne Klimberg, MD[7], Mariana Chavez-MacGregor, MD[8], Gary Freedman, MD[9], Nehmat Houssami, MD, PhD[10], Peggy L. Johnson[11], and Monica Morrow, MD[12]

- The panel commissioned a systematic review and meta-analysis of the literature as the primary evidence base for the guideline.

- 21 studies from 1965 to 2010. All data reviewed by 2 independent investigators.

- A study-level analysis was conducted, adjusted for study-specific median follow-up time (to account for the inherent increased risk of IBTR with longer follow-up) as well as covariates.

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Ann Surg Oncol (2014) 21:717–730

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	Number in model		Model estimates adjusted for study-specific median follow-up time		
	Subjects	LR	Odds of LR (odds ratio)	95 % CI	*P* value[a] [*P* for trend]
Model 1 (median study-specific median follow-up time 6.6 years)	28,162	1,506	–	–	
Margin status					<0.001
Negative	21,984	1,005	1.0	–	
Positive/close	6,178	501	1.96	1.72–2.24	
Threshold distance for negative margins[b]					0.12 [0.21[c]]
>0 mm	2,898	167	1.47	0.67–3.20	
1 mm	6,008	422	1.0	–	
2 mm	11,144	530	0.95	0.54–1.67	
5 mm	8,112	386	0.65	0.34–1.26	
Model 2 (median study-specific median follow-up time 8.7 years)	13,081	753	–	–	–
Margin status					<0.001
Negative	9,033	393	1.0	–	
Close	2,407	176	1.74	1.42–2.15	
Positive	1,641	184	2.44	1.97–3.03	
Threshold distance for negative margins[b]					0.90 [0.58]
1 mm	2,376	235	1.0	–	
2 mm	8,350	414	0.91	0.46–1.80	
5 mm	2,355	103	0.77	0.32–1.87	

OR = 1,74 in patients with close margins: is really negligible?

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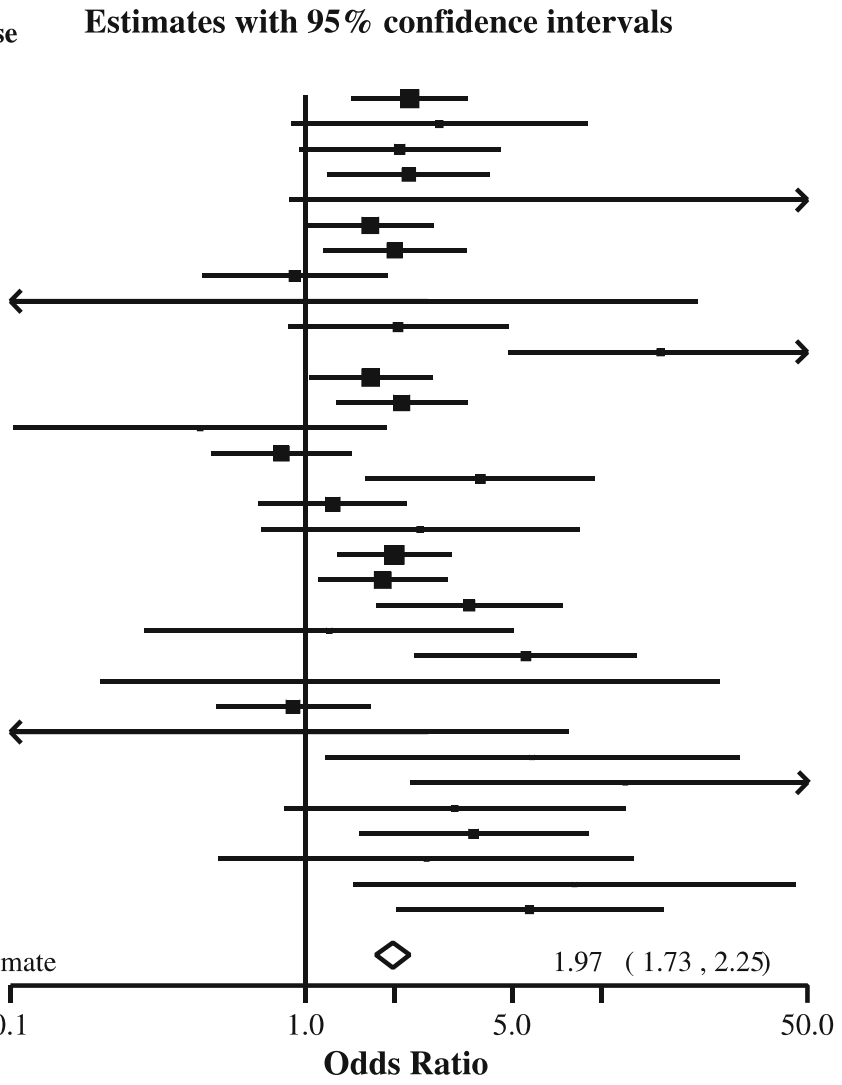
ORIGINAL ARTICLE – GUIDELINE AND META-ANALYSIS

The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis

Nehmat Houssami, MD, PhD[1], Petra Macaskill, PhD[1], M. Luke Marinovich, MPH[1], and Monica Morrow, MD[2]

[1]Screening and Test Evaluation Program (STEP), School of Public Health (A27), Sydney Medical School, University of Sydney, Sydney, Australia; [2]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Study	Publication year	Follow-up (months)	Negative n/N	Positive/Close n/N
Kreike	2008	160	41/485	44/256
Obedian	1999	156	6/278	6/102
Bellon	2005	135	12/123	18/98
Park	2000	127	14/204	41/286
Neuschatz	2003	121	0/69	27/288
Santiago	2004	121	48/455	30/184
Voogd	2001	118	35/468	23/165
Demirci	2012	118	32/789	10/268
Varghese	2008	111	4/68	0/7
Mirza	2002	108	76/722	7/36
Goldstein	2003	104	3/333	34/269
Ewertz	2008	102	226/3455	20/192
Livi	2007	89	85/2590	19/284
Touboul	1999	87	52/417	2/34
Groot	2011	86	56/500	19/201
Leong	2004	80	20/352	8/42
Perez	2003	79	38/787	18/305
Kasumi	2006	78	3/307	16/680
McBain	2003	77	72/1265	30/279
Freedman	1999	76	47/968	25/294
Lupe	2011	62	23/1980	11/273
Livi	2013	62	39/2007	2/86
Smitt	2003	60	10/342	12/83
Whipp	2010	60	1/114	2/102
Karasawa	2005	59	16/256	39/684
Liau	2010	58	5/461	0/97
Kunos	2006	56	2/222	6/119
Horiguchi	2002	54	2/176	5/41
Pierce	1997	53	11/363	3/33
Kokubo	2000	52	9/675	11/231
Karasawa	2003	52	3/249	3/99
Burke	1995	50	5/290	2/16
Spivack	1994	48	8/214	8/44



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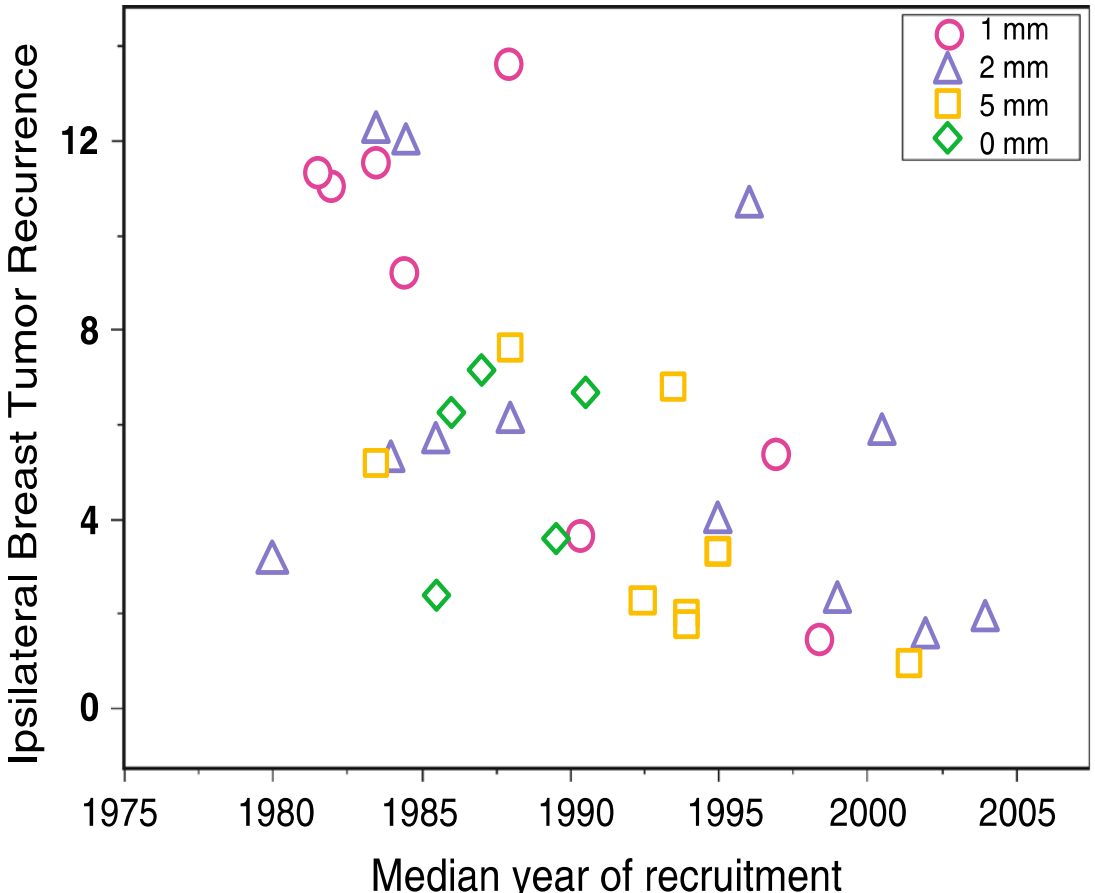
the crude incidence of IBTR declined over time, and although this was observed for all margin widths, the decline appeared more pronounced in those with margins less than 5 mm.

The benefits of adjuvant systemic therapy in reducing IBTR are well documented.



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- A positive margin is defined as the presence of ink at the surface of the surgical specimen on either invasive tumor cells or DCIS and implies a potentially incomplete resection that is associated with a significantly higher risk of IBTR. There is no debate regarding this concept.

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Radiation Therapy Delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width.

In summary, margin width should not be used to determine the delivery technique or fractionation for WBRT or vice versa. Furthermore, in patients with negative margins (no ink on tumor), the use and dose of a tumor bed boost should be based on a priori estimation of local failure risk and should not be determined, in isolation, by the width of the surgical margin.

J Clin Oncol. 2007 Aug 1;25(22):3259-65. Epub 2007 Jun 18.

Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial.

Bartelink H1, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, Jager JJ, Hoogenraad WJ, Oei SB, Wárlám-Rodenhuis CC, Pierart M, Collette L.

"These data suggest that although a boost provides a degree of reduction in IBTR when margins are microscopically positive, the absolute benefit is not sufficient to reduce the rate of IBTR to that seen with negative margins and the use of a boost."

Similarly the effects of a positive margin do not appear to be negated by the use of either adjuvant endocrine therapy or chemotherapy.

Radiother Oncol. 2013 Aug;108(2):273-8. doi: 10.1016/j.radonc.2013.02.009
Epub 2013 Mar 13.

Radiotherapy boost dose-escalation for invasive breast cancer after breast-conserving surgery: 2093 patients treated with a prospective margin-directed policy.

Livi L, Meattini I, Franceschini D, Saieva C, Meacci F, Marrazzo L, Gerlain E, Desideri I, Scotti V, Nori J, Sanchez LJ, Orzalesi L, Bonomo P, Greto D, Bianchi S, Biti G.

CONCLUSIONS:
Our experience showed that a margin-directed policy of RT boost dose-escalation seems to reduce the negative impact of FMS on LR, but it is not able to overcome the unfavorable effect of higher nuclear grade, higher T stage and triple negative subtype.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

RTOG 9804: A Prospective Randomized Trial for Good-Risk Ductal Carcinoma In Situ Comparing Radiotherapy With Observation

Beryl McCormick, Kathryn Winter, Clifford Hudis, Henry Mark Kuerer, Eileen Rakovitch, Barbara L. Smith, Nour Sneige, Jennifer Moughan, Amit Shah, Isabelle Germain, Alan C. Hartford, Afshin Rashtian, Eleanor M. Walker, Albert Yuen, Eric A. Strom, Jeannette L. Wilcox, Laura A. Vallow, William Small Jr, Anthony T. Pu, Kevin Kerlin, and Julia White

See accompanying article doi: 10.1200/JCO.2014.59.4259

Stratify	Age 1. < 50 2. ≥ 50 Final Path Margins 1. Negative (re-excision) 2. 3-9 mm 3. ≥ 10 mm Mammographic/Pathologic Size of Primary 1. ≤ 1 cm 2. > 1 cm to ≤ 2.5 cm Nuclei Grade 1. Low 2. Intermediate Tamoxifen Use 1. No 2. Yes	Randomize	Arm 1 Observation with or without tamoxifen 20 mg per day for 5 years Arm 2 Radiation therapy* to the whole breast, with or without tamoxifen 20 mg per day for 5 years

RT: 50 Gy in 25
50,4 Gyin 28

No boost

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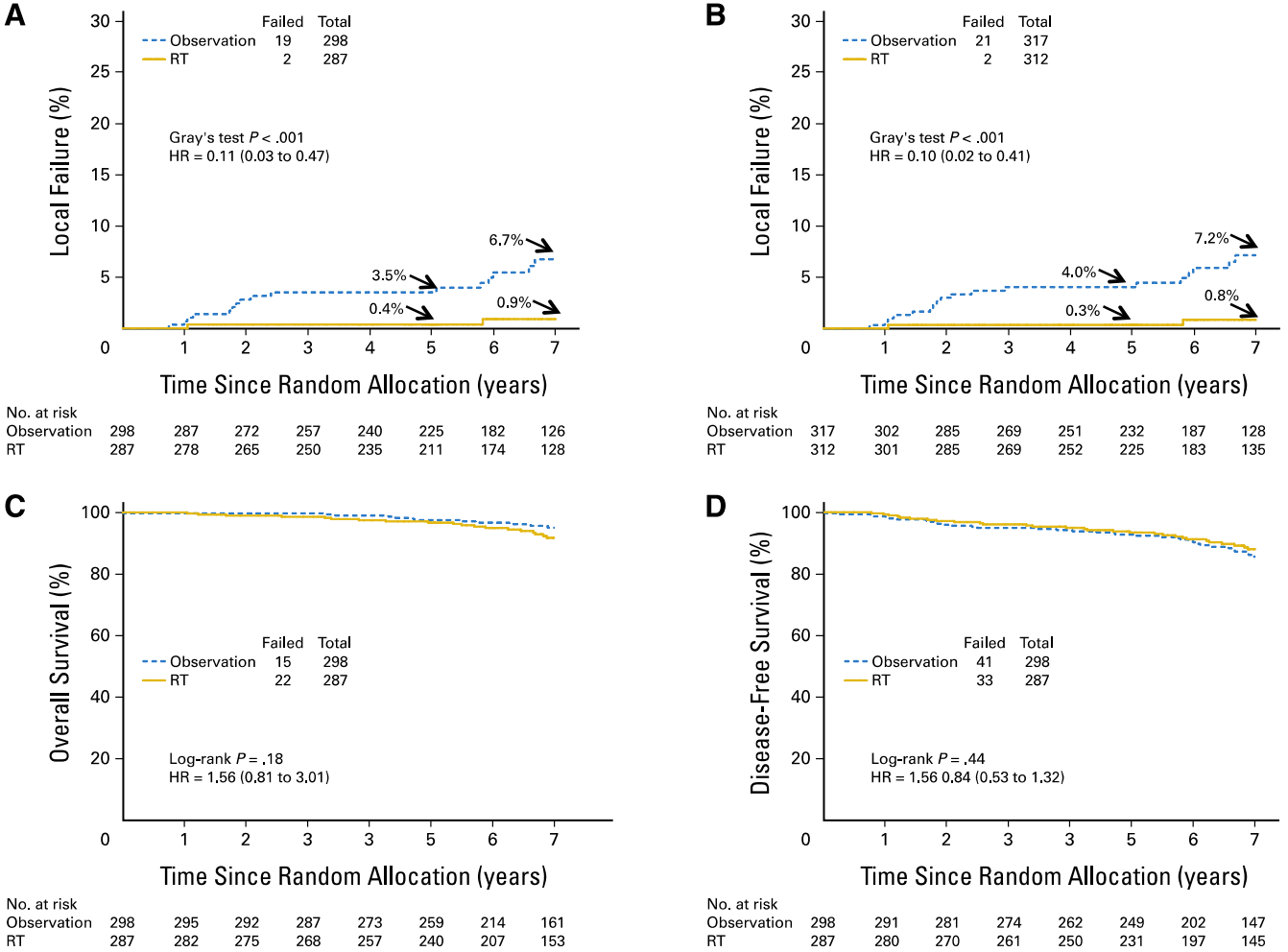

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effect of Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma in Situ: 20 Years Follow-Up in the Randomized SweDCIS Trial

Fredrik Wärnberg, Hans Garmo, Stefan Emdin, Veronica Hedberg, Linda Adwall, Kerstin Sandelin, Anita Ringberg, Per Karlsson, Lars-Gunnar Arnesson, Harald Anderson, Karin Jirström, and Lars Holmberg

PORT in patients undergoing BCS is not able to nullify the negative effect of the positive margin.

The benefit of PORT in reducing the IBRs is more evident in patients over 52 aa., conferming the importance of young age as indipendent risk factor

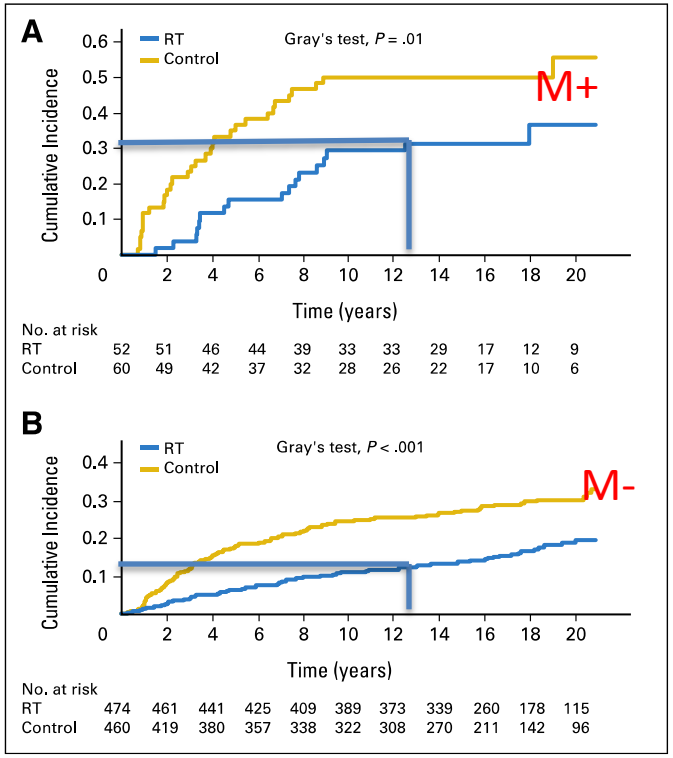

Fig 3. Cumulative incidence of all ipsilateral new breast cancer events in SweDCIS (Swedish Ductal Carcinoma in Situ) trial by treatment (breast-conserving surgery plus radiotherapy [RT] arm v control arm) for women (A) without and (B) with clear margins (including those with missing data).

What we take home?

- Close margin is not a risk factor for LR;
- No reason to intensify Rt doses (to Wb or as boost)in close margins;
- Patients with positive margins will never have the same low risk as negative margins ones (not with RT nor with CT).
- Negative margin doesn’t mean “no tumor cells” in residual breast.
- Biological factors must be taken in account scheduling therapeutic programs.

THM

- “Adherence to guidelines reduce costs and guarantee the best treatment for the patients”……..is always true?

- Tailoring treatments on th basis of guidelines could be a good solution (“nani sulle spalle dei giganti”)

Reading literature to have more doubts